UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/512,001	09/08/2005	Alcide Barberis	27656/40537	2325

4743 7590 03/20/2008
MARSHALL, GERSTEIN & BORUN LLP
233 S. WACKER DRIVE, SUITE 6300
SEARS TOWER
CHICAGO, IL 60606

EXAMINER	
KETTER, JAMES S	

ART UNIT	PAPER NUMBER
1636	

MAIL DATE	DELIVERY MODE
03/20/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/512,001	BARBERIS ET AL.	
	Examiner	Art Unit	
	James S. Ketter	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,10,15 and 17* is/are rejected.

7)☒ Claim(s) *7-9,11-14,16 and 18-22* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 October 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/26/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Applicant's election without traverse of the species of APP beta-site and secretase in the reply filed on 7 December 2007 is acknowledged.

Claims 7-9, 11-14, 16 and 18-22 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 6, 10, 15 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dyrks et al. (cited on the IDS filed 26 November 2004 as reference D) in view of Lam et al. (N, newly cited).

Claim 1 is drawn to a method for the identification/isolation of modulators of a secretase activity wherein suitable eukaryotic host cells are contacted with a test substance wherein said suitable host cells comprise: a) a fusion protein comprising a secretory protein, a membrane anchor domain and a secretase cleavage sequence, b) a protein comprising a secretase activity recognizing said cleavage sequence of said fusion protein and c) at least one reporter gene under control of a transcriptional activation system wherein said transcriptional activation system is regulated by the release of said secretory protein from said fusion protein by said secretase activity and its subsequent secretion then culturing said cells under suitable conditions such tat said reporter gene allowing detection and/or survival of cells is only expressed or repressed in a manner that is dependent on an altered secretase activity due to said test substance. Claim 2 specifies within claim 1 that a reduced or no release of said secretory protein due to a reduced/inhibited secretase activity leads to expression of said at least one reporter gene thereby allowing detection and/or survival of cells under suitable culturing conditions. Claim 3 specifies within claim 1 that said at least one reporter gene is selected from genes conferring antibiotic resistance, genes encoding reporter molecules with an activity that can be detected by colorimetric or fluorescent methods and genes complementing auxotrophies. Claim 6 specifies within claim 1 that said cells comprise a second reporter gene selected from the group consisting of: a) genes encoding reporter molecules with an activity that can be detected by colorimetric or fluorescent methods, b) genes conferring antibiotic resistance and genes conferring sensitivity to

a chemical and c) genes complementing auxotrophies. Claim 10 specifies within claim 1 that said secretase cleavage sequence is selected from the beta site and the alpha site of the human amyloid precursor protein and the beta site of Notch 1 protein. Claim 15 specifies within claim 1, wherein a nucleic acid construct encoding said fusion protein is integrated into the genome of said host cell. Claim 17 specifies within claim 1 that said secretase activity is selected from beta-secretase and alpha-secretase.

Dyrks et al. teaches, e.g., at page 3, a process for the quantitative and differential determination of the APP secretases involved in amyloid betaA4 release and for the direct isolation of corresponding modulators is described which is characterized in that a) first of all a suitable expression vector is prepared by i) recombinant fusion of the secretory form of a protein, which secretory form is fused to the recognition sites for APP alpha- or beta-secretase, with ii) a suitable transmembrane anchor sequence, and iii) expression under the control of a suitable promoter, b) eukaryotic cells are stably transfected with the expression vector so produced, c) the transfected cells are selected with a suitable marker, d) the selected stable cells are analysed immunologically or enzymatically by means of the secreted reporter domain using current standard methods and finally e) with the use of suitable vectors as negative and positive controls, the modulators that stimulate or inhibit the alpha- or beta-secretase activity are determined. Dyrks et al. differs from the claimed invention in not teaching the use of this method for assaying modulators of the secretase activity.

Lam et al. teaches, e.g., at the Abstract, a method of using a chimeric protein for detecting presence or activity of a pre-determined protease, which protein comprises a repressor domain that represses activity of a biologically active protein fused to it, and a reporter domain

comprising a protein with biological activity when not fused to the repressor domain, and a protease cleavage domain linking the first two domains. The protein comprises a site cleaved by activity of the protease. At, e.g., page 4, first full paragraph, Lam et al. teaches the use of the system and method to screen for compounds that affect the amount or activity of the protease.

It would have been obvious to one of skill in the art to have practiced the method of Dyrks et al. including an assay step for compounds that affect the protese/secretase activity, as taught by Lam et al. As both Dyrks et al. and Lam et al. use an assay system whereby a reporter protein is activated by cleavage from the fusion protein, it would have been expected by one of ordinary skill in the art that the compound screening assay taught by Lam et al. would have been functional in the method of Dyrks et al., retaining the same function and activity.

Claims 1, 4 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dyrks et al. in view of Lam et al., and in further view of Nandabalan et al. (A, newly cited).

Claim 1 is described above. It is included in the instant rejection as it encompasses the embodiments of claims 4 and 5, which depend therefrom. Claim 4 specifies within claim 1 that the release of the secretory protein due to an enhanced secretase activity leads to a reduced expression of said at least one reporter gene thereby allowing detection and/or survival of cells under suitable conditions. Claim 5 specifies within claim 4 that the reporter gene is selected from genes conferring sensitivity to a chemical.

Dyrks et al. and Lam et al. are described in the rejection set forth above. Both of Dyrks et al. and Lam et al differ from the claimed invention in not teaching the use of a negatively-

selectable reporter, i.e., wherein cleavage of the fusion protein and therefore expression of the reporter is selected against.

Nandabalan et al. teaches, e.g., at the paragraph bridging columns 17 and 18, and at the paragraph bridging columns 18 and 19, the use of negative selection, particularly using Can1 or Cyh1, and that negative selection can help to avoid false positive results.

It would have been obvious to one of ordinary skill in the art to have practiced the method of Dyrks et al. including an assay step for compounds that affect the protese/secretase activity, as taught by Lam et al., using negative selection as taught by Nandabalan et al. As both Dyrks et al. and Lam et al. use an assay system whereby a reporter protein is activated by cleavage from the fusion protein, it would have been expected by one of ordinary skill in the art that the compound screening assay taught by Lam et al. would have been functional in the method of Dyrks et al., retaining the same function and activity. The motivation to use negative selection would have come from Nandabalan et al., in teaching that false positive results would be reduced.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James S. Ketter whose telephone number is 571-272-0770. The examiner can normally be reached on Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

JSK
21 March 2008

/James S. Ketter/
Primary Examiner, Art Unit 1636